Br. J. clin. Pharmac. (1992), **34**, 11–20

Medical management of hypercalcaemia

S. H. RALSTON
Department of Medicine and Therapeutics, Aberdeen University Medical School, Foresterhill Hospital, Aberdeen AB9 2ZD

1 Hypercalcaemia is a common disorder, which frequently requires specific treatment either to control symptoms, or to prevent the development of irreversible organ damage or death. Although the best and most effective way of controlling hypercalcaemia in the long-term is to treat the underlying cause, medical antihypercalcaemic therapy is often required in clinical practice, either as a holding measure, or because the primary disease cannot itself be treated.

2 The mainstays of medical antihypercalcaemic therapy are firstly, to promote calcium excretion by the kidney by restoring extracellular volume with intravenous saline and secondly, to administer pharmacological agents which inhibit bone resorption. Measures which seek to reduce intestinal calcium absorption are seldom effective.

3 Intravenous bisphosphonates are the treatment of first choice for the initial management of hypercalcaemia, followed by continued oral, or repeated intravenous bisphosphonates to prevent relapse. These drugs have a relatively slow onset of action (1–3 days) but have potent and sustained inhibitory effects on bone resorption, resulting in a long duration of action (12–30 days).

4 Of the other agents available, calcitonin has an important place in the management of severe hypercalcaemia where a rapid effect is desirable; calcitonin is best used in conjunction with a bisphosphonate however, because of its short duration of action. Intravenous phosphate also has a place in the emergency management of severe hypercalcaemia, but is probably best reserved for patients in whom other less toxic therapies have failed. Corticosteroids are generally ineffective except in certain specific instances and are best avoided in the routine treatment of undiagnosed hypercalcaemia.

Presentation

Hypercalcaemia can occur in association with a wide variety of underlying disorders, although the vast majority of hypercalcaemic patients seen in routine clinical practice turn out to have one of two disorders; primary hyperparathyroidism or malignant disease (Fisken *et al.*, 1980) (Table 1).

With the increasing use of autoanalyser technology, the most common mode of presentation of hypercalcaemia nowadays is as an 'isolated' laboratory abnormality, picked up on routine biochemical screening. Many patients however, also exhibit symptoms or signs related to the elevation in serum calcium levels (Mundy, 1989; Warwick *et al.*, 1961). The symptoms of hypercalcaemia (Table 2) are wide-ranging but relatively non-specific; since they are usually superimposed on those of the underlying disorder, symptomatic deterioration may be erroneously attributed to the primary disease process (such as advancing cancer, for example), rather than the elevation in serum calcium values. In general, hypercalcaemic symptoms increase in proportion to the degree of elevation in serum calcium values, although there is considerable inter-individual variation, such that some patients—particularly those with cancer-

Table 1 Frequency with which different causes of hypercalcaemia are seen in clinical practice

Very commonly	Cancer Primary hyperparathyroidism
Rarely	Sarcoidosis Immobilisation Thyrotoxicosis Vitamin D toxicity Thiazide-induced Acute renal failure (recovery phase)
Very rarely	Addison's disease Non-sarcoid granulomatous disease Familial hypocalciuric hypercalcaemia Milk-alkali syndrome

Correspondence: Dr S. H. Ralston, Department of Medicine and Therapeutics, Aberdeen University Medical School, Foresterhill Hospital, Aberdeen AB9 2ZD

Table 2 Symptoms and signs of hypercalcaemia

Kidney	*Gut*	*CNS*	*CVS*	*Other*
polyuria; polydipsia; thirst; renal failure; nephrocalcinosis; nephrolithiasis*	anorexia; nausea; vomiting; constipation; pancreatitis*	confusion; coma; depression (Fitz & Hallman, 1952); ataxia (Streeto, 1969); scotomata (Simpson, 1954); localising neurological signs (Mundy, 1989); reduced pain threshold (Mundy & Martin, 1982); muscle weakness, hypotonia, fatigue (Patten *et al.*, 1974).	hypertension (Weidmann *et al.*, 1972); arrythmia (Bronsky *et al.*, 1961); ECG changes (Bronsky *et al.*, 1961); increased sensitivity to digoxin (Bower & Mengle, 1936)	conjunctivitis; corneal calcification; vascular calcification.

*Rare in cancer-associated hypercalcaemia.
Selected symptoms and signs are referenced.

related hypercalcaemia—may experience severe symptoms with relatively mild hypercalcaemia. In most cases the symptoms of hypercalcaemia can be reversed, either partially or completely, by effective antihypercalcaemic therapy (Ralston *et al.*, 1990a), although it is important to note that the rate of symptomatic improvement may lag behind the biochemical response.

Investigation and differential diagnosis

Since most hospital laboratories measure total serum calcium concentration, it is frequently necessary to 'correct' the measured calcium concentration for the prevailing level of serum albumin (Editorial, 1977; Payne *et al.*, 1979). This is because approximately half of the total calcium is in the biologically active ionised form, while most of the remainder is bound to albumin. In the presence of hypoalbuminaemia therefore, total calcium concentrations may be normal or low, when the ionised (and biologically relevant) fraction is in fact elevated (Iqbal *et al.*, 1988). While 'correcting' the total calcium level for albumin serves to compensate for such variation in plasma protein binding in most cases, patients with paraproteinaemia may occasionally present with spurious hypercalcaemia, due to excessive binding of calcium by the circulating globulins (Merlini *et al.*, 1984). In this situation, the diagnosis of hypercalcaemia can only confidently be made or excluded by measurement of ionised (or diffusible) calcium.

The most useful investigation in differential diagnosis of hypercalcaemia is determination of plasma immunoreactive parathyroid hormone levels (iPTH) (Brown *et al.*, 1987; Editorial, 1985; Logue *et al.*, 1990). In patients with elevated or 'innappropriately detectable' iPTH values, primary hyperparathyroidism is the most likely diagnosis provided that the rare condition of familial hypocalciuric hypercalcaemia is excluded by assessment of fasting urinary calcium excretion (Menko *et al.*, 1983). While cases of true 'ectopic PTH' production have been described in cancer, this is extremely rare and the finding of a raised iPTH level in a hypercalcaemic patient with cancer is much more likely to be due to co-existent primary hyperparathyroidism. Patients with non-parathyroid causes of hypercalcaemia such as malignant disease, vitamin D intoxication, sarcoidosis, and immobilisation tend to have low or undetectable iPTH values (Logue *et al.*, 1990). Although full discussion of the differential diagnosis of these conditions is beyond the scope of this article, two points deserve mention; firstly, patients with cancer-associated hypercalcaemia, who comprise the vast majority of this group, can usually be diagnosed at the bedside, since most have advanced tumours by the time hypercalcaemia develops. Secondly, a very rapid indication of the aetiology of hypercalcaemia can often be gained by measurement of serum albumin, since the presence of hypo-albuminaemia strongly favours the diagnosis of cancer-related hypercalcaemia.

Mechanisms of hypercalcaemia

Whatever the underlying cause, hypercalcaemia is due to a disturbance in homeostatic mechanisms regulating calcium exchange at three sites; the kidney, bone, and the intestine (Parfitt, 1979). The relative importance of these in the pathogenesis of hypercalcaemia is discussed below.

Kidney

Abnormalities of renal calcium homeostasis are of crucial importance in the pathogenesis and maintenance of most types of hypercalcaemia. Hypercalcaemia acts directly on the renal tubule to cause inappropriate urinary loss of sodium and water (Benabe & Martinez-Maldonado, 1978; Gill & Bartter, 1969), which may not be replaced as the result of gastro-intestinal symptoms. The state of volume contraction and sodium depletion resulting from the above is associated with renal sodium retention; this further reduces urinary calcium excretion by stimulating calcium reabsorption in the proximal renal tubule, since the transport of these two ions are linked at this site (Benabe & Martinez-Maldonado, 1978; Lassiter *et al.*, 1963). In some conditions, such as primary hyperparathyroidism and many cancers, the reabsorption of calcium in the distal renal tubule is also increased (Peacock *et al.*, 1969; Ralston *et al.*, 1984) due, respectively, to the effects of PTH (Agus *et al.*, 1973; Peacock *et al.*, 1969) and PTH-related peptide (PTHrP) (Horiuchi *et al.*, 1987; Kemp *et al.*, 1987).

In addition to the renal tubular abnormalities discussed above, impairment of glomerular filtration rate is common in hypercalcaemic patients as the result of dehydration and sodium depletion (Benabe & Martinez-Maldonado, 1978), irreversible renal tubular and glomerular damage as the result of prolonged hypercalcaemia, or in association with the excretion of specific nephrotoxic substances such as Bence-Jones protein in myeloma (Mundy & Martin, 1982).

Bone

Bone resorption is increased in the majority of patients with severe hypercalcaemia and in most cases, this increase is due to stimulation of osteoclastic activity (Parfitt, 1979). Osteoclasts are multinucleated cells which act to remove calcified bone matrix during the normal process of bone remodelling (Chambers, 1985). In many hypercalcaemic disorders, osteoclastic bone resorption is increased, either on a systemic basis, due to the action of circulating humoral factors (e.g. PTH, PTHrP, vitamin D metabolites, thyroid hormones) or in association with local release of osteoclast-stimulating factors by tumour metastases (Mundy & Martin, 1982). While increased bone resorption alone is often insufficient to cause hypercalcaemia because of compensatory homeostatic mechanisms (Peacock *et al.*, 1969; Ralston *et al.*, 1984) the abnormalities of renal function which are frequently operative in hypercalcaemic states impair the ability of the kidney to increase calcium excretion, so allowing serum calcium levels to rise.

Intestine

Intestinal calcium absorption is increased in a variety of hypercalcaemic disorders including primary hyperparathyroidism, sarcoidosis, vitamin D intoxication and some lymphomas (Davies *et al.*, 1985; Mawer *et al.*, 1985; Parfitt, 1979; Singer & Adams, 1986). While this process contributes to the pathogenesis of hypercalcaemia in some cases, it is often overshadowed by the contribution of kidney and bone, not least because of the fact that patients with hypercalcaemia severe enough to require treatment are usually anorexic and taking little in the way of dietary calcium in any case!

Antihypercalcaemic treatment

At the outset it should be emphasised that the only sure way of controlling hypercalcaemia in the long-term is to identify and treat the underlying cause; this may involve surgical parathyroidectomy in hyperparathyroidism; chemotherapy or radiotherapy in cancer-associated hypercalcaemia; steroid therapy in sarcoidosis and so on. In some patients however, effective therapy for the underlying disease may not be available; in others, the underlying cause of hypercalcaemia may not be known, or specific treatment may have to be delayed because of co-existent medical problems. It is in these circumstances that medical antihypercalcaemic therapy is indicated.

Successful medical management depends on correcting the abnormalities of renal, skeletal and intestinal calcium homeostasis which contribute to the hypercalcaemia. In most cases, this requires drug therapy to inhibit osteoclastic bone resorption and intravenous fluid therapy to promote the urinary excretion of calcium. Reducing dietary calcium intake, or giving agents which will inhibit intestinal calcium absorption are much less effective in the treatment of hypercalcaemia probably because the contribution of increased intestinal absorption is in most cases, overshadowed by abnormalities of renal function and bone resorption.

Specific agents

Intravenous fluid

Rehydration with intravenous fluid is an important aspect of antihypercalcaemic therapy (Heller & Hosking, 1986; Hosking *et al.*, 1981). Initially, 500 ml 0.9% saline should be given every 4–6 h intravenously and the infusion continued for 2–3 days. This regimen should be sufficient to replace the sodium and water deficit in most patients and will in addition, be enough to stimulate a sodium-linked calcium diuresis in the proximal renal tubule (Hosking *et al.*, 1981). Subsequently, saline infusions of approximately 2 l day^{-1} should be continued to maintain the urine output until serum calcium values are below 3.0 mmol l^{-1} and/or an adequate oral fluid intake has been established. Loop diuretics such as frusemide (40–80 mg every 2–4 h) have been used, in combination with very large quantities of saline (12–14 l day^{-1}) in the treatment of severe hypercalcaemia (Suki *et al.*, 1970). Although effective, this treatment may be associated with serious haemodynamic and electrolyte disturbances and its use demands intensive care facilities with close monitoring of urinary electrolyte losses and central venous pressure monitoring. Loop diuretics should not however, be used routinely during rehydration except for fluid overload, since there is a risk that they may actually impair calcium excretion by perpetuating a state of extracellular volume contraction.

Saline repletion alone may be expected to reduce serum calcium values by 0.2–0.4 mmol l^{-1} on average and in some cases may restore normocalcaemia (Heller & Hosking, 1986; Hosking *et al.*, 1981; Sleeboom *et al.*, 1983). Further drug therapy aimed at reducing bone resorption is usually necessary to achieve a sustained response however, since accelerated bone resorption is almost always present in patients with severe hypercalcaemia.

Calcitonin

Calcitonin is a valuable adjunct to rehydration in the initial management of severe hypercalcaemia. It has a rapid calcium-lowering effect, evident within 2 h of administration, due to inhibitory effects on osteoclastic activity and renal tubular reabsorption of calcium (Hosking & Gilson, 1984; Silva & Becker, 1973; Wisneski *et al.*, 1978). The effect of calcitonin on renal handling of calcium is probably due in part, to its natriuretic effect (Bijvoet *et al.*, 1971). Salmon calcitonin is usually employed in the treatment of hypercalcaemia because it is more potent than both human and porcine calcitonins; various regimens have been used, although the dose-response relationship seems to be relatively flat above 25–50 i.u. 8-hourly by subcutaneous injection (Hosking & Gilson, 1984).

The response to calcitonin, while rapid in onset, is usually short lived and many patients 'escape' control after 2–3 days, due to down-regulation of calcitonin receptors on the osteoclast. It has been found that in some cases, such relapses may be partly prevented by the co-administration of corticosteroids (e.g. prednisolone 40 mg day^{-1}) (Binstock & Mundy, 1980), although in many patients with cancer-associated hypercalcaemia, the addition of steroids makes little difference to the response (Warrell *et al.*, 1988). In the longer term, this combination of drugs provides less complete control of hypercalcaemia than the bisphosphonates or mithramycin (Ralston *et al.*, 1985). Recently, calcitonin has been sucessfully combined with the bisphosphonate disodium pamidronate in the treatment of cancer-associated hypercalcaemia, since its rapid effect was useful in controlling hypercalcaemia during the first 24–48 h of treatment, while the bisphosphonate had time to take effect (Ralston *et al.*, 1986).

Intravenous phosphate

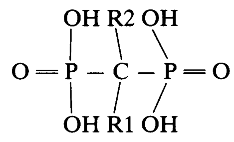
Intravenous neutral phosphate (40 mmol infused slowly over 4–6 h) is an effective treatment for most types of hypercalcaemia (Fulmer *et al.*, 1972; Goldsmith & Ingbar, 1966). Serum calcium values start to fall within a few minutes of administration, due to precipitation of insoluble calcium-phosphate complexes in bone and soft tissues, although subsequently, there may be an inhibitory effect on osteoclastic bone resorption (Herbert *et al.*, 1966). The duration of action is relatively brief and in most patients, serum calcium values start to rise once again after 2–3 days (Fulmer *et al.*, 1972).

While intravenous phosphate is almost invariably effective, serious adverse effects such as hypotension, ectopic calcification and acute renal failure may occur, particularly in patients with pre-existing renal dysfunction and hyperphosphataemia (Breuer & Le Bauer, 1967; Carey *et al.*, 1968). Because of the above problems, intravenous phosphate is probably best reserved for patients with life-threatening hypercalcaemia in whom other treatments have failed.

Mithramycin

Mithramycin is a cytotoxic antibiotic, initially used as a chemotherapeutic agent in certain solid tumours (Kennedy, 1970). It is an effective antihypercalcaemic agent at one tenth of the doses used for antitumour therapy (Perlia *et al.*, 1970; Ralston *et al.*, 1985; Singer *et al.*, 1970), because of its inhibitory effects on osteoclastic activity (Kiang *et al.*, 1979; Ralston *et al.*, 1985) and renal tubular reabsorption of calcium (Ralston *et al.*, 1985). Mithramycin is generally administered as a single intravenous injection of 25 μg kg^{-1} body weight. Depending on the response, the drug may be repeated on two or more occasions. Lowering of serum calcium values reliably occurs within 24 h of administration, with a maximal effect at 2–4 days and a duration of action of 9–10 days (Ralston *et al.*, 1985). Normocalcaemia is restored at some point in approximately 30–40% of treated patients (Ralston *et al.* 1985; Sleeboom & Bijvoet, 1985). Although effective, repeated use of mithramycin is limited by toxicity (Kennedy, 1970); in addition to causing nausea, vomiting and malaise directly after administration, potentially serious side effects such as thrombocytopaenia, renal damage and liver damage may also occur, particularly with repeated doses. Because of these adverse effects, mithramycin has largely been superseded by other agents with a more favourable toxicity profile (Ralston *et al.*, 1985).

Table 3 Structure of bisphosphonates



Etidronate = R1 – OH, R2 – CH3
Clodronate = R1 – Cl, R2 – Cl
Pamidronate = R1 – OH, R2 – CH2 – CH2 – NH2

Bisphosphonates

The bisphosphonates are a group of compounds which share in common, potent inhibitory effects on osteoclastic bone resorption (Fleisch, 1983, 1989). Structurally, the bisphosphonates are characterised by a central core of P-C-P atoms, to which are attached various chemical side chains; these determine the potency and specific properties of individual compounds in the group (Table 3).

While bisphosphonates may be given orally in the treatment of hypercalcaemia, intravenous administration is preferred initially at least, because of the common occurrence of nausea and vomiting in hypercalcaemic patients, coupled with the bisphosphonates' poor and unpredictable intestinal absorption (Fleisch, 1989). Although many bisphosphonates have been synthesised (see reviews by Fleisch (1983, 1989)), only three are currently available in the UK for clinical use and further discussion will be confined to the use of these compounds; etidronate (ethane hydroxy bisphosphonate), clodronate (dichloromethylene bisphosphonate) and pamidronate (aminohydroxypropylidene bisphosphonate).

Etidronate

Etidronate has been almost exclusively used in the treatment of cancer-associated hypercalcaemia. Although early investigators used repeated daily doses of between 200 mg–1000 mg etidronate by intravenous injection (Jung, 1982), it is now given by slow intravenous infusion (7.5 mg kg^{-1} body weight) for 3 consecutive days (Hasling *et al.*, 1987; Jacobs *et al.*, 1987; Kanis *et al.*, 1987; Ralston *et al.*, 1989; Ryzen *et al.*, 1985a,b). Serum calcium values start to fall within 2–3 days after starting treatment with a maximal effect between days 6–7 (Hasling *et al.*, 1987; Jacobs *et al.*, 1987; Jung, 1982; Kanis *et al.*, 1987; Ralston *et al.*, 1989; Ryzen *et al.*, 1985a,b). The supressive effect on serum calcium values lasts about 10–12 days (Ralston *et al.*, 1989; Ringerberg & Ritch, 1987; Ryzen *et al.*, 1985a). Although most patients respond to intravenous etidronate, normocalcaemia is restored in only 15–40% of treated patients (Kanis *et al.*, 1987; Ralston *et al.*, 1989; Ryzen *et al.*, 1985a). Higher rates of 'normocalcaemia'—between

75%–90% – have been reported in some studies (Jung, 1982; Hasling *et al.*, 1987; Ryzen *et al.*, 1985b) but these are rather misleading in that they have been based on a reduction in total rather than albumin-adjusted serum calcium values to normal; since hypercalcaemic cancer patients are almost invariably hypoalbuminaemic however, these reports have probably overestimated the efficacy of etidronate (Kanis *et al.*, 1987).

Oral etidronate is relatively ineffective as a primary treatment for hypercalcaemia (Mundy *et al.*, 1983) but does appear to prolong the effect of intravenous etidronate (Ringerberg & Ritch, 1987). In one study, cancer patients who were rendered normocalcaemic by intravenous etidronate relapsed after a mean of 30 days post treatment when given oral etidronate also (20 mg kg^{-1} day^{-1}), compared with 12 days in patients given intravenous etidronate alone (Ringerberg & Ritch, 1987).

Adverse effects to intravenous etidronate are rare, although a disturbance in taste sensation has been reported in some cases (Jones *et al.*, 1987). While acute renal failure has been recorded in patients with severe hypercalcaemia who were given high doses of etidronate (1000 mg) by rapid intravenous infusion (Bounameaux *et al.*, 1983), this complication has not been reported using the lower doses in current clinical use. Since prolonged etidronate therapy has been associated with the development of drug-induced osteomalacia in Paget's disease (Boyce *et al.*, 1984), it is currently recommended that the duration of therapy be limited to 30 days. In cancer-associated hypercalcaemia (by far the most common reason for giving antihypercalcaemic drugs), this is a theoretical rather than practical drawback, since few patients survive beyond 3 months (Ralston *et al.*, 1990a).

Clodronate

Clodronate is a more potent inhibitor of bone resorption than etidronate *in vitro* (Fleisch, 1983; 1989) and in clinical studies has been found to be more effective than etidronate in restoring normocalcaemia (Kanis *et al.*, 1990; Ralston *et al.*, 1989; Ryzen *et al.*, 1985b). Like etidronate, clodronate has mainly been used in the treatment of cancer-associated hypercalcaemia (Adami *et al.*, 1987; Bonjour *et al.*, 1988; Chapuy *et al.*, 1980; Jacobs *et al.*, 1981; Paterson *et al.*, 1983; Rastad *et al.*, 1987; Shane *et al.*, 1982; Witte *et al.*, 1987), although there are reports of its successful use in hypercalcaemia associated with immobilisation (Yates *et al.*, 1984) and hypercalcaemia due to primary and tertiary hyperparathyroidism (Douglas *et al.*, 1980; Hamdy *et al.*, 1987; Shane *et al.*, 1981). Many dose regimens of clodronate have been tried ranging from slow intravenous infusions of 300–1500 mg on a single occasion (Adami *et al.*, 1987; Bonjour *et al.*, 1988; Ralston *et al.*, 1989; Witte *et al.*, 1987), to repeated daily infusions of 300–600 mg to total doses in excess of 3 g (Adami *et al.*, 1987; Jacobs *et al.*, 1981; Jung, 1982; Kanis *et al.*, 1990; Rastad *et al.*, 1987; Shane *et al.*, 1982; Witte *et al.*, 1987).

There are no good studies on the optimal dose of clodronate in the treatment of cancer-associated hypercalcaemia and many regimens have been used in clinical practice; some investigators have reported little or no difference between single infusions of 500–600 mg and repeated infusions of 300 mg daily for between 5–10 days (Adami *et al.*, 1987; Bonjour *et al.*, 1988), whereas others have found that, in certain groups of patients, a total dose of 1500 mg, given either as a single infusion over 24 h or as repeated infusions of 300 mg for 5 days are more effective than single doses of 600 mg (Kanis *et al.*, 1990). Currently, the manufacturers of clodronate recommend a regimen of 300 mg given daily for 5 days.

Serum calcium values start to fall within 2–3 days of starting clodronate, with a nadir at day 5–6 and a duration of action of approximately 10–12 days. Reported rates of normocalcaemia in hypercalcaemic cancer patients treated with intravenous clodronate range from 40%–75% in different series (Adami *et al.*, 1987; Bonjour *et al.*, 1988; Jacobs *et al.*, 1981; Kanis *et al.*, 1990; Ralston *et al.*, 1989). As with many other antihypercalcaemic agents (Gurney *et al.*, 1989; Ralston *et al.*, 1987), tumour type has been identified as an important factor in determining the rate of response to clodronate (Bonjour *et al.*, 1988; Kanis *et al.*, 1990), in that patients with local osteolytic type hypercalcaemia (e.g. myeloma), respond far better than do those with humorally-mediated hypercalcaemia (e.g. lung carcinoma). Intravenous clodronate is generally well tolerated, although acute renal failure has been recorded in an isolated patient with severe hypercalcaemia who was given high doses (19.9 g over 30 days) by repeated intravenous infusions (Bounameaux *et al.*, 1983). Renal impairment has not been recorded with the doses currently used in clinical practice.

Oral clodronate has been successfully used in the primary treatment of cancer-associated hypercalcaemia (Chapuy *et al.*, 1980; Paterson *et al.*, 1983; Percival *et al.*, 1985; Rastad *et al.*, 1987) and hypercalcaemic primary hyperparathyroidism (Douglas *et al.*, 1980; Hamdy *et al.*, 1987), but is more commonly employed as an adjunct to intravenous clodronate therapy to prevent relapse of hypercalcaemia (Adami *et al.*, 1987; Rastad *et al.*, 1987). The recommended doses range from 1600 mg–3200 mg daily, depending on the individual response. Although doses of up to 2400 mg are generally well-tolerated, gastro-intestinal side effects—particularly diarrhoea—occur quite frequently (in between 40%–80% of cases) with higher doses (Siris *et al.*, 1983, 1980).

Pamidronate

Pamidronate is the most potent bisphosphonate clinically available (Fleisch, 1983, 1989). It has been successfully used in the treatment of a wide variety of hypercalcaemic disorders including cancer-associated hypercalcaemia (Body *et al.*, 1986; Cantwell & Harris, 1987; Coleman & Rubens, 1987; Davis & Heath, 1989; Harinck *et al.*, 1987b; Ralston *et al.*, 1989; Sleeboom *et al.*, 1983), thyrotoxicosis (Tan *et al.*, 1988), immobilisation (McIntyre *et al.*, 1989), sarcoidosis (Gibbs & Peacock, 1986), hypercalcaemia following renal transplantation (Leunissen *et al.*, 1986) and primary hyperparathyroidism (Evans, 1987; van Breukelen *et al.*, 1982). In common with the other bisphosphonates, the onset of action is relatively slow, and 1–2 days may elapse before serum calcium values start to fall after intravenous administration (Ralston *et al.*, 1988; Sleeboom *et al.*, 1983; Yates *et al.*, 1987). The nadir of serum calcium is usually reached by day 5–6, with a duration of action of between 20–30 days (Morton *et al.*, 1988; Ralston *et al.*, 1988, 1989).

Many regimens of pamidronate have been used in clinical practice, ranging from repeated daily infusions of 15 mg to a cumulative total of 90 mg (Ralston *et al.*, 1986; Sleeboom *et al.*, 1983; Yates *et al.*, 1987), to single intravenous infusions of between 5 mg–90 mg (Morton *et al.*, 1988; Ralston *et al.*, 1988, 1989; Thiebaud *et al.*, 1986a; Yates *et al.*, 1987). Since there appears to be no significant advantage with repeated administration (Morton *et al.*, 1988; Ralston *et al.*, 1988; Yates *et al.*, 1987), single infusions are most commonly used in clinical practice. Dose-ranging studies in cancer-associated hypercalcaemia have shown that the dose-response curve is relatively flat above 15–30 mg (Body *et al.*, 1987; Ralston *et al.*, 1988), although higher doses may be required in selected patients with resistant hypercalcaemia—particularly those who have received previous courses of antihypercalcaemic drugs (Judson *et al.*, 1990; Morton *et al.*, 1990).

While the manufacturers recommend that the dose of pamidronate should be titrated to the severity of hypercalcaemia, there is little objective evidence to support this viewpoint (Davis & Heath, 1989; Gallacher *et al.*, 1992; Gurney *et al.*, 1989).

Randomised clinical studies have shown that intravenous pamidronate is superior to standard regimens of mithramycin and corticosteroid/calcitonin in the treatment of cancer-associated hypercalcaemia, both with respect to the degree of reduction in serum calcium and the duration of action (Ralston *et al.*, 1985). Furthermore, in a recent study, a single dose of 30 mg pamidronate was also found to be superior to standard doses of etidronate and a single intravenous dose of 600 mg clodronate in this situation, both with respect to calcium-lowering effect and duration of action (Ralston *et al.*, 1989). It has been argued that the dose of clodronate used in the above study may have been suboptimal (Kanis *et al.*, 1990) although the same comments might also apply to the dose of pamidronate (Morton *et al.*, 1990; Ralston *et al.*, 1990). It is currently unknown how maximal doses of clodronate (1500 mg) would compare with maximal doses of pamidronate (90 mg).

Intravenous pamidronate is well tolerated, although a transient leukopaenia and mild pyrexia (usually asymptomatic) may occur in some cases (Gallacher *et al.*, 1989; Harinck *et al.*, 1987a).

Oral pamidronate has been used successfully in the primary treatment of hypercalcaemia (Thiebaud *et al.*, 1986b; van Breukelen *et al.*, 1982), but at the time of writing, the oral preparation is not yet available for clinical use in the UK.

Oral phosphate

Oral neutral phosphate is an effective treatment for hypercalcaemia (Goldsmith & Ingbar, 1966; Thallasinos & Joplin, 1968). By raising serum phosphate concentrations, oral phosphate acts, like intravenous phosphate, to promote precipitation of insoluble calcium phosphate complexes in bone and soft tissues and to inhibit osteoclastic activity (Herbert *et al.*, 1966). Oral phosphate also acts to reduce intestinal calcium absorption, and this may be relevant in the treatment of hypercalcaemic disorders where absorption of calcium from the gut is increased (e.g. vitamin D toxicity, sarcoidosis, primary hyperparathyroidism).

Although phosphate is often effective, the doses required (2–3 g daily) are poorly tolerated due to gastrointestinal upset and diarrhoea, thus limiting its usefulness.

Corticosteroids

Corticosteroids have long been used in the treatment of hypercalcaemia, particularly that associated with malignant disease (Myers, 1958). Response of cancer-associated hypercalcaemia to corticosteroid therapy however, is often incomplete and unpredictable (Percival *et al.*, 1984; Thalassinos & Joplin, 1970), unless the primary tumour is itself steroid responsive (e.g. myeloma/lymphoma). Hypercalcaemia associated with vitamin D toxicity usually responds to steroid therapy, probably because of reduced intestinal calcium absorption (Verenr *et al.*, 1958), as does the hypercalcaemia of sarcoidosis, largely due to its disease-modifying effect (Anderson *et al.*, 1954; Singer & Adams, 1986). While primary hyperparathyroid patients seldom respond to steroid treatment (forming the basis of the now outdated steroid suppression test (Dent, 1956), some patients with parathyroid bone disease do respond (Watson *et al.*, 1980).

In view of their rather unpredictable effects, corticosteroids should not be used as a 'blanket' treatment for undiagnosed hypercalcaemia or for the hypercalcaemia of malignancy. They remain useful however, for the specific indications discussed above.

Other treatments

Gallium nitrate is now widely used in the USA for the treatment of cancer associated hypercalcaemia and in clinical studies has been shown to have an overall degree of efficacy comparable with that of the more potent bisphosphonates. It acts by inhibiting osteoclastic bone resorption and like the bisphosphonates, has a slow onset of action (2–3 days) with a maximal effect between days 6–8 post treatment (Warrell *et al.*, 1983, 1984, 1988, 1990). Although the drug may cause renal impairment, the risk of this is relatively low, provided the patient is kept well hydrated and other nephrotoxic drugs (e.g. aminoglycosides) are avoided (Warrell *et al.*, 1988). It is not yet available in the UK for routine clinical use.

Prostaglandin synthetase inhibitors such as indomethacin have been used in the treatment of cancer-associated hypercalcaemia, on the basis of their inhibitory effect on bone resorption stimulated by certain experimental tumour models *in vitro* (Seyberth *et al.*, 1975; Tashjian, 1975). Although some patients with cancer-associated hypercalcaemia have been shown to respond to these agents (Seyberth *et al.*, 1975), most workers have been disappointed by their lack of effect (Brenner *et al.*, 1982; Mundy *et al.*, 1983) and they cannot generally be recommended for the treatment of cancer-associated hypercalcaemia, or other types of hypercalcaemia.

The somatostatin analogue ocreotide has recently been successfully used in the treatment of hypercalcaemia associated with certain neuroendocrine tumours (Harrison *et al.*, 1990; Wynick *et al.*, 1990). The mechanism of action is as yet unclear, although in one case reported to date, the drug may have worked by reducing 'ectopic' secretion of PTHrP by the tumour (Wynick *et al.*, 1990). It is not yet known whether this, or related drugs may prove to be of value in the treatment of other types of hypercalcaemia.

The antimalarial drugs chloroquine and hydroxychloroquine may be used in the treatment of hypercalcaemia associated with sarcoidosis, where they exert a supressive effect on the primary disease process (Singer & Adams, 1986). These agents are not effective in other types of hypercalcaemia.

Haemodialysis or peritoneal dialysis against a low calcium dialysate (e.g. 1.25 mM), may be used transiently to reduce serum calcium values in hypercalcaemic patients with renal failure (Miach *et al.*, 1975). Unfortunately, its effect is relatively transient, and is essentially used as a holding measure, while other more specific treatments are taking effect.

References

Adami, S., Bolzicco, G. P., Rizzo, A., Salvagno, G., Bertoldo, F., Rossini, M., Suppi, R. & Lo Cascio, V. (1987). The use of dichloromethylene bisphosphonate and aminobutane bisphosphonate in hypercalcemia of malignancy. *Bone and Mineral*, **2**, 395–404.

Agus, A. Z., Gardner, L. B., Beck, L. H. & Goldberg, M. (1973). Effects of parathyroid hormone on renal tubular reabsorption of calcium, sodium and phosphate. *Am. J. Physiol.*, **224**, 1143–1148.

Anderson, J. C., Dent, C. E., Harper, C. & Philpot, G. R. (1954). Effect of cortisone on calcium metabolism in sarcoidosis with hypercalcaemia: possible antagonistic actions of cortisone and vitamin D. *Lancet*, **ii**, 720–724.

Benabe, J. E. & Martinez-Maldonado, M. (1978). Hypercalcemic nephropathy. *Arch. int. Med.*, **138**, 777–779.

Bijvoet, O. L. M., van der Sluys Veer, J., de Vreis, H. & van Koppen, A. I. J. (1971). Natriuretic effect of calcitonin in man. *New Engl. J. Med.*, **284**, 681–688.

Binstock, M. L. & Mundy, G. R. (1980). Effect of calcitonin and glucocorticoids in combination on the hypercalcemia of malignancy. *Ann. intern. Med.*, **93**, 269–272.

Body, J. J., Borkowski, A., Cleeren, A. & Bijvoet, O. L. M. (1986). Treatment of malignancy-associated hypercalcemia with intravenous aminohydroxypropylidene diphosphonate. *J. clin. Oncol.*, **4**, 1177–1183.

Body, J. J., Pot, M., Borkowski, A., Sculier, J. P. & Klastersky, J. (1987). Dose-response study of aminohydroxypropylidene bisphosphonate in tumor-associated hypercalcemia. *Am. J. Med.*, **82**, 957–963.

Bonjour, J.-P., Guelpa, P. G., Bisetti, A., Rizzoli, R., Jung, A., Rosini, S. & Kanis, J. A. (1988). Bone and renal components of hypercalcemia of malignancy and response to a single infusion of clodronate. *Bone*, **9**, 123–130.

Bounameaux, H. M., Schifferli, J., Montani, J.-P., Jung, A. & Chatelanat, F. (1983). Renal failure associated with intravenous diphosphonates. *Lancet*, **i**, 471.

Bower, J. O. & Mengle, H. A. K. (1936). The additive effect of calcium and digitalis. *J. Am. med. Ass.*, **106**, 1151–1153.

Boyce, B. F., Smith, M. L., Fogelman, I., Johnston, E., Ralston, S. & Boyle, I. T. (1984). Focal osteomalacia due to low-dose diphosphonate therapy in Paget's disease. *Lancet*, **i**, 821–824.

Brenner, D. E., Harvey, H. A., Lipton, A. & Demers, L. (1982). A study of prostaglandin E_2, parathormone and response to indomethacin in patients with hypercalcemia of malignancy. *Cancer*, **49**, 556–561.

Breuer, R. I. & Le Bauer, J. (1967). Caution in the use of phosphates in the treatment of severe hypercalcemia. *J. clin. Endocrinol. Metab.*, **27**, 695–698.

Bronsky, D., Dubin, A., Kushner, D. S. & Waldstein, S. S. (1961). Calcium and the electrocardiogram. III. The relationship of the intervals of the electrocardiogram to the level of serum calcium. *Am. J. Cardiol.*, **7**, 840–843.

Brown, R. C., Aston, J. P., Weeks, I. & Woodhead, J. S. (1987). Circulating intact parathyroid hormone measured by a two-site immunochemiluminometric assay. *J. clin. Endocrinol. Metab.*, **65**, 407–413.

Cantwell, B. M. J. & Harris, A. L. (1987). Effect of single high dose infusions of aminohydroxypropylidene diphosphonate on hypercalcaemia caused by cancer. *Br. med. J.*, **294**, 467–469.

Carey, R. W., Schmitt, G. W., Kopald, H. H. & Kantrowitz, P. A. (1968). Massive extraskeletal calcification during phosphate treatment of hypercalcemia. *Arch. intern. Med.*, **122**, 150–155.

Chambers, T. J. (1985). The pathiobiology of the osteoclast. *J. clin. Path.*, **38**, 241–252.

Chapuy, M. C., Meunier, P. J., Alexandre, C. M. & Vignon, E. P. (1980). Effects of disodium dichloromethylene diphosphonate on hypercalcemia produced by bone metastases. *J. clin. Invest.*, **65**, 1243–1247.

Coleman, R. E. & Rubens, R. D. (1987). (3-amino-1,1-hydroxypropylidene) bisphosphonate for hypercalcaemia of breast cancer. *Br. J. Cancer*, **56**, 465–469.

Davies, M., Hayes, M. E., Mawer, E. B. & Lumb, G. A. (1985). Abnormal vitamin D metabolism in Hodgkin's lymphoma. *Lancet*, **ii**, 1186–1188.

Davis, J. R. E. & Heath, D. A. (1989). Comparison of different dose regimens of aminohydroxypropylidene-1,1-bisphosphonate (APD) in hypercalcaemia of malignancy. *Br. J. clin. Pharmac.*, **28**, 269–274.

Dent, C. E. (1956). Cortisone test for hyperparathyroidism. *Br. med. J.*, **1**, 230–233.

Douglas, D. L., Duckworth, T., Russell, R. G. G., Kanis, J. A., Preston, C. J., Preston, F. E., Prenton, M. A. & Woodhead, J. S. (1980). Effect of dichloromethylene diphosphonate in Paget's disease of bone and in hypercalcaemia due to primary hyperparathyroidism or malignant disease. *Lancet*, **i**, 1043–1047.

Editorial (1977). Correcting the calcium. *Br. med. J.*, **1**, 598.

Editorial (1985). Determining the cause of hypercalcaemia. *Lancet*, **i**, 376–377.

Evans, R. A. (1987). Aminohydroxypropylidene diphosphonate treatment of hypercalcaemic crisis due to primary hyperparathyroidism. *Aust. N.Z. J. Med.*, **17**, 58–59.

Fisken, R. A., Heath, D. A. & Bold, A. M. (1980). Hypercalcaemia—a hospital survey. *Quart. J. Med.*, **49**, 405–418.

Fitz, T. E. & Hallman, B. L. (1952). Mental changes associated with hyperparathyroidism. *Arch. intern. Med.*, **89**, 547–551.

Fleisch, H. (1983). Bisphosphonates: mechanisms of action and clinical applications. In *Bone and mineral research*, ed. Peck, W. A., pp. 319–357. Amsterdam: Exerpta Medica.

Fleisch, H. (1989). Bisphosphonates—mechanisms of action. In *Disodium pamidronate (APD) in the treatment of malignancy-related disorders*, ed. Burckhardt, P., pp. 21–35. Toronto: Hans Huber.

Fulmer, D. H., Dimich, A. B., Rothschild, E. O. & Myers,

W. P. L. (1972). Treatment of hypercalcaemia: comparison of intravenously administered phosphate, sulphate and hydrocortisone. *Arch. intern. Med.*, **129**, 923–930.

Gallacher, S. J., Ralston, S. H., Patel, U. & Boyle, I. T. (1989). Side effects of pamidronate. *Lancet*, **ii**, 42–43.

Gallacher, S. J., Ralston, S. H., Fraser, W. D., Dryburgh, F. J., Cowan, R. A., Logue, F. C. & Boyle, I. T. (1992). A comparison of low versus high dose pamidronate in cancer-associated hypercalcaemia. *Bone and Mineral* (in press).

Gibbs, C. J. & Peacock, M. (1986). Hypercalcaemia due to sarcoidosis corrects with bisphosphonate treatment. *Postgrad. med. J.*, **62**, 937–938.

Gill, J. R. & Bartter, F. C. (1969). On the impairment of renal concentrating ability in prolonged hypercalcemia and hypercalciuria in man. *Nephron*, **6**, 50–61.

Goldsmith, R. S., Ingbar, S. H. (1966). Inorganic phosphate treatment of hypercalcemia of diverse aetiologies *New Engl. J. Med.*, **274**, 1–7.

Gurney, H., Kefford, R. & Stuart-Harris, R. (1989). Renal phosphate threshold and response to pamidronate in humoral hypercalcaemia of malignancy. *Lancet*, **i**, 241–244.

Hamdy, N. A. T., Gray, R. E. S., McCloskey, E., Galloway, J., Rattenbury, J. M., Brown, C. B. & Kanis, J. A. (1987). Clodronate in the medical management of hyperparathyroidism. *Bone*, **8** (suppl. 1), s69–s77.

Harinck, H. I. J., Bijvoet, O. L. M., Platingh, A. S. T., Body, J. J., Elte, J. W. F., Sleeboom, H. P., Wildiers, J. & Neijt, J. P. (1987b). Role of bone and kidney in tumor induced hypercalcemia and its treatment with bisphosphonate and sodium chloride. *Am. J. Med.*, **82**, 1133–1142.

Harinck, H. I. J., Papapoulos, S. E., Blanksma, H. J., Moolenar, A. J., Vermeij, P. & Bijvoet, O. L. M. (1987a). Paget's disease of bone: early and late responses to three different modes of treatment with aminohydroxypropylidene bisphosphonate (APD). *Br. med. J.*, **295**, 1301–1305.

Harrison, M., James, N., Broadley, K., Bloom, S. R., Armour, R., Wimalawansa, S., Heath, D. & Waxman, J. (1990). Somatostatin analogue treatment for malignant hypercalcaemia. *Br. med. J.*, **300**, 1313–1314.

Hasling, C., Charles, P. & Mosekilde, L. (1987). Etidronate disodium in the management of malignancy-related hypercalcemia. *Am. J. Med.*, **62** (suppl.), 51–54.

Heller, S. R. & Hosking, D. J. (1986). Renal handling of calicum and sodium in metastatic and non-metastatic malignancy. *Br. med. J.*, **292**, 583–586.

Herbert, L. A., Lemann, J., Petersen, J. R. & Lennon, E. J. (1966). Studies of the mechanism by which phosphate infusion lowers serum calcium concentration. *J. clin. Invest.*, **45**, 1886–1894.

Horiuchi, N., Caulfield, M. P., Fisher, J. E., Goldman, M. E., McKee, R. L., Reagan, J. E., Levy, J. J., Nutt, R. F., Rodan, S. B., Schofield, T. L. Clemens, T. L. & Rosenblatt, M. (1987). Similarity of synthetic peptide of a parathyroid hormone-related protein to parathyroid hormone *in vivo* and *in vitro*. *Science*, **238**, 1566–1567.

Hosking, D. J., Cowley, A. & Bucknall, C. A. (1981). Rehydration in the treatment of severe hypercalcaemia. *Quart. J. Med.*, **200**, 473–481.

Hosking, D. J. & Gilson, D. (1984). Comparison of the renal and skeletal actions of calcitonin in the treatment of severe hypercalcaemia of malignancy. *Quart. J. Med.*, **211**, 359–368.

Iqbal, S. J., Giles, M., Ledger, S., Nanji, N. & Howl, T. (1988). Need for albumin adjustments of urgent total serum calcium. *Lancet*, **ii**, 1477–1478.

Jacobs, T. P., Gordon, A. C., Silverberg, S. J., Shane, E., Reich, L., Clemens, T. L., & Gundberg, C. M. (1987). Neoplastic hypercalcemia: physiologic response to intravenous etidronate disodium. *Am. J. Med.*, **62** (suppl.), 42–50.

Jacobs, T. P., Siris, E. S., Bilezikian, J. P., Baquiran, D. C., Shane, E. & Canfield, R. E. (1981). Hypercalcaemia of malignancy: Treatment with intravenous dichloromethylene diphosphonate. *Ann. intern. Med.*, **94**, 312–316.

Jones, P. B. B., McCloskey, E. V. & Kanis, J. A. (1987). Transient taste-loss during treatment with etidronate. *Lancet*, **ii**, 637.

Judson, I., Booth, F., Gore, M. & McElwain, T. (1990). Chronic high-dose pamidronate in refractory malignant hypercalcaemia. *Lancet*, **335**, 802.

Jung, A. (1982). Comparison of two parenteral diphosphonates in hypercalcaemia of malignancy. *Am. J. Med.*, **72**, 221–226.

Kanis, J. A., McCloskey, E. V. & Paterson, A. H. G. (1990). Use of diphosphonates in hypercalcaemia due to malignancy. *Lancet*, **335**, 170–171.

Kanis, J. A., Urwin, G. H., Gray, R. E. S., Beneton, M. N. C., McCloskey, E. V., Hamdy, N. A. T. & Murray, S. A. (1987). Effects of intravenous etidronate disodium on skeletal and calcium metabolism. *Am. J. Med.*, **62** (suppl.), 55–70.

Kemp, B. E., Moseley, J. M., Rodda, C. P., Ebeling, P. R., Wettenhall, R. E. H., Stapleton, D., Diefenbach-Jagger, H., Ure, F., Michelangeli, V. P., Simmonds, H. A., Raisz, L. G. & Martin, T. J. (1987). Parathyroid hormone-related protein of malignancy: active synthetic fragments. *Science*, **238**, 1568–1570.

Kennedy, B. J. (1970). Metabolic and toxic effects of mithramycin during tumor therapy. *Am. J. Med.*, **49**, 494–503.

Kiang, D. T., Loken, M. K. & Kennedy, B. J. (1979). Mechanism of the hypocalcemic effect of mithramycin. *J. clin. Endocrinol. Metab.*, **48**, 341–344.

Lassiter, W. E., Gottschalk, C. W. & Mylle, M. (1963). Micropuncture study of renal tubular reabsorption of calcium in normal rodents. *Am. J. Physiol.*, **204**, 771–775.

Leunissen, K. M. L., Vismans, F. J. F., van Leendert, R. J. M. & van Hooff, J. P. (1986). Successful treatment of persistent posttransplant hyperparathyroidism with bisphosphonate. *Transplantation*, **41**, 666–667.

Logue, F. C., Beastall, G. F., Fraser, W. D. & O'Reilly, D.StJ. (1990). Intact parathyroid hormone assays. *Br. med. J.*, **300**, 210–211.

Mawer, E. B., Hann, J. T., Berry, J. L. & Davies, M. (1985). Vitamin D metabolism in patients intoxicated with ergocalciferol. *Clin. Sci.*, **68**, 141–145.

McIntyre, H. D., Cameron, D. P., Urquhart, S. M. & Davies, W. E. (1989). Immobilization hypercalcaemia responding to intravenous pamidronate therapy. *Postgrad. med. J.*, **65**, 244–246.

Menko, F. H., Bijvoet, O. L. M., Fronen, J. L. H. H., Sandler, L. M., Adami, S., O'riordan, J. L. H. & Blomen-Kukenen, W. (1983). Familial benign hypercalcaemia. *Quart. J. Med.*, **206**, 120–140.

Merlini, G., Fitzpatrick, L. A., Siris, E. S., Bilezikian, J. P., Birken, S., Beychok, S. & Osserman, E. F. (1984). A human myeloma immunoglobulin G binding four moles of calcium associated with asymptomatic hypercalcemia. *J. clin. Immunol.*, **4**, 185–196.

Miach, P. J., Dawborn, J. K., Martin, T. J. & Moon, W. J. (1975). Management of the hypercalcemia of malignancy by peritoneal dialysis. *Med. J. Aust.*, **1**, 782–784.

Morton, A. R., Cantrill, J. A., Craig, A. E., Howell, A., Davies, M. & Anderson, D. C. (1988). Single dose versus daily intravenous aminohydroxypropylidene bisphosphonate (APD) for the hypercalcaemia of malignancy. *Br. med. J.*, **296**, 811–814.

Morton, A. R., Freifeld, J. & Halperin, F. (1990). Dose of bisphosphonate for hypercalcaemia of malignancy. *Lancet*,

335, 1469–1470.

Mundy, G. R. (1989). Clinical features and differential diagnosis of hypercalcemia. In *Calcium homeostasis: hypercalcemia and hypocalcemia*, pp. 51–63. London: Dunitz.

Mundy, G. R. & Martin, T. J. (1982). The hypercalcemia of malignancy: pathogenesis and management. *Metabolism*, **131**, 1247–1277.

Mundy, G. R., Wilkinson, R. & Heath, D. A. (1983). Comparative study of the available medical therapy for hypercalcaemia of malignancy. *Am. J. Med.*, **74**, 421–432.

Myers, W. P. L. (1958). Cortisone in the treatment of hypercalcaemia in neoplastic disease. *Cancer*, **11**, 83–88.

Parfitt, A. M. (1979). Equilibrium and disequilibrium hypercalcemia. New light on an old concept. *Metab. Bone Dis. rel. Res.*, **1**, 279–293.

Paterson, A. D., Kanis, J. A., Cameron, E. C., Douglas, D. L., Beard, D. J., Preston, F. E., & Russell, R. G. G. (1983). The use of dichloromethylene diphosphonate for the management of hypercalcaemia in multiple myeloma. *Br. J. Haematol.*, **54**, 121–132.

Patten, B. M., Bilezikian, J. P., Mallette, L. E., Prince, A., Engel, W. K. & Aurbach, G. D. (1974). Neuromuscular disease in primary hyperparathyroidism. *Ann. intern. Med.*, **80**, 182–193.

Payne, R. B., Carrer, R. B. & Morgan, D. B. (1979). Interpretation of serum total calcium: effects of adjustment for albumin concentration on frequency of abnormal values and detection of changes in individual. *J. clin. Path.*, **32**, 50–60.

Peacock, M., Robertson, W. G. & Nordin, B. E. C. (1969). Relation between serum and urinary calcium with particular reference to parathyroid activity. *Lancet*, **i**, 384–386.

Percival, R. C., Yates, A. J. P., Gray, R. E. S., ?? (1984). Role of glucocorticoids in the management of malignant hypercalcaemia. *Br. med. J.*, **289**, 287–288.

Percival, R. C., Paterson, A. D., Yates, A. J. P., Beard, D. J., Douglas, D. L., Neal, F. E., Russell, R. G. G. & Kanis, J. A. (1985). Treatment of malignant hypercalcaemia with clodronate. *Br. J. Cancer*, **51**, 665–669.

Perlia, C. P., Gubisch, N. J. H., Wolter, J., Edelberg, D., Dederick, D. D. & Taylor, S. G. (1970). Mithramycin treatment of hypercalcemia. *Cancer*, **25**, 389–394.

Ralston, S. H., Alzaid, A. A., Gallacher, S. J., Gardner, M. D., Cowan, R. A. & Boyle, I. T. (1988). Clinical experience with aminohydroxypropylidene bisphosphonate (APD) in the management of cancer-associated hypercalcaemia. *Quart. J. Med.*, **258**, 825–834.

Ralston, S. H., Alzaid, A. A., Gardner, M. D., & Boyle, I. T. (1986). Treatment of cancer-associated hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin. *Br. med. J.*, **292**, 1549–1550.

Ralston, S. H., Cowan, R. A., McKillop, J. H., Gardner, M. D. & Boyle, I. T. (1987). Mechanisms of hypercalcaemia and response to antihypercalcemic therapy in malignancy. *Bone and Mineral*, **2**, 227–242.

Ralston, S. H., Fogelman, I., Gardner, M. D., Dryburgh, F. J., Cowan, R. A. & Boyle, I. T. (1984). Hypercalcaemia of malignancy: evidence for a non-parathyroid humoral mediator with an effect on renal tubular calcium handling. *Clin. Sci.*, **66**, 187–191.

Ralston, S. H., Gardner, M. D., Dryburgh, F. J., Jenkins, A. S., Cowan, R. A. & Boyle, I. T. (1985). Comparison of aminohydroxypropylidene diphosphonate, mithramycin and corticosteroids/calcitonin in treatment of cancer associated hypercalcaemia. *Lancet*, **ii**, 907–910.

Ralston, S. H., Gallacher, S. J., Patel, U., Campbell, J. & Boyle, I. T. (1990a). Cancer-associated hypercalcemia: morbidity and mortality. *Ann. intern. Med.*, **112**, 499–504.

Ralston, S. H., Gallacher, S. J., Patel, U., Dryburgh, F. J., Fraser, W. D., Cowan, R. A. & Boyle, I. T. (1989). Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. *Lancet*, **ii**, 1180–1182.

Ralston, S. H., Gallacher, S. J., Patel, U., Dryburgh, F. J., Fraser, W. D., Cowan, R. A. & Boyle, I. T. (1990b). Use of bisphosphonates in hypercalcaemia due to malignancy. *Lancet*, **335**, 737.

Rastad, J., Benson, L., Johansson, H., Knuutila, M., Pettersson, B., Wallfelt, C., Akerstrom, G. & Ljunghall, S. (1987). Clodronate treatment in patients with malignancy-associated hypercalcemia. *Acta med. Scand.*, **221**, 489–494.

Ringerberg, Q. S. & Ritch, P. S. (1987). Efficacy of oral administration of etidronate disodium in maintaining normal serum calcium levels in previously hypercalcemic cancer patients. *Clin. Ther.*, **9**, 1–7.

Ryzen, E., Martodam, R. R., Troxell, M., Benson, A., Paterson, A., Shepard, K. & Hicks, R. (1985b). Intravenous etidronate in the management of malignant hypercalcemia. *Arch. int. Med.*, **145**, 449–452.

Ryzen, E., Rude, R. K., Elbaum, N. & Singer, F. R. (1985a). Use of intravenous etidronate disodium in the treatment of hypercalcemia. In *Bone resorption, metastasis and diphosphonates*, ed. Garatini, S., pp. 99–108. New York: Raven Press.

Seyberth, H. W., Segre, G. V., Morgan, J. L., Sweetman, B. J., Potts, J. T. & Oates, J. A. (1975). Prostaglandins as mediators of hypercalcaemia associated with certain types of cancer. *New Engl. J. Med.*, **293**, 1278–1283.

Shane, E., Baquiran, D. C. & Bilezikian, J. P. (1981). Effects of dichloromethylene diphosphonate on serum and urinary calcium in primary hyperparathyroidism. *Ann. intern. Med.*, **95**, 23–27.

Shane, E., Jacobs, T. P., Siris, E. S., Steinberg, S. F., Stoddart, K., Canfield, R. E. & Bilezikian, J. P. (1982). Therapy of hypercalcaemia due to parathyroid carcinoma with intravenous dichloromethylene diphosphonate. *Am. J. Med.*, **72**, 939–944.

Silva, O. M. & Becker, K. L. (1973). Salmon calcitonin in the treatment of hypercalcemia. *Arch. Int. Med.*, **132**, 337–339.

Simpson, J. A. (1954). Aphonia and deafness in hyperparathyroidism. *Br. med. J.*, **1**, 494–496.

Singer, F. R. & Adams, J. S. (1986). Abnormal calcium homeostasis in sarcoidosis. *New Engl. J. Med.*, **315**, 755–757.

Singer, F. R., Neer, R. M., Murray, T. M., Keutmann, H. T., Deftos, L. J. & Potts, J. T. (1970). Mithramycin treatment of intractible hypercalcemia due to parathyroid carcinoma. *New Engl. J. Med.*, **283**, 634.

Siris, E., Hyman, G. A. & Canfield, R. E. (1983). Effects of dichloromethylene diphosphonate in women with breast carcinoma metastatic to the skeleton. *Am. J. Med.*, **74**, 401–406.

Siris, E., Sherman, W. H., Baquiran, D. C., Schlatterer, J. P., Osserman, E. F. & Canfield, R. E. (1980). Effects of dichloromethylene diphosphonate on skeletal mobilisation of calcium in multiple myeloma. *New Engl. J. Med.*, **302**, 310–315.

Sleeboom, H. P. & Bijvoet, O. L. M. (1985). Treatment of tumour-induced hypercalcaemia. In *Bone resorption, metastasis and diphosphonates*, ed. Garatini, S., pp. 59–78. New York: Raven Press.

Sleeboom, H. P., Bijvoet, O. L. M., Van Oosterom, A. T., Gleed, J. H. & O'Riordan, J. L. H. (1983). Comparison of intravenous (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate and volume repletion in tumour-induced hypercalcaemia. *Lancet*, **ii**, 239–243.

Streeto, J. M. (1969). Acute hypercalcemia simulating basilar artery insufficiency. *New Engl. J. Med.*, **280**, 427–429.

Suki, W. N., Yium, J. J., Von Linden, M., Saller-Herbert, C., Eknoyan, G. & Martinez-Maldonado, M. (1970). Acute treatment of hypercalcemia with furosemide. *New Engl. J. Med.* **283**, 836–840.

Tan, T. T., Alzaid, A. A., Sutcliffe, N., Gardner, M. D., Thomson, J. A. & Boyle, I. T. (1988). Treatment of hypercalcaemia in thyrotoxicosis with aminohydroxypropylidene diphosphonate. *Postgrad. med. J.*, **64**, 224–227.

Tashjian, A. H. (1975). Tumor humors and the hypercalcemia of cancer. *New Engl. J. Med.*, **293**, 1317–1318.

Thalassinos, N. J. & Joplin, G. F. (1970). Failure of corticosteroid therapy to correct the hypercalcaemia of malignant disease. *Lancet*, **ii**, 537–539.

Thallasinos, N. J. & Joplin, G. F. (1968). Phosphate treatment of hypercalcaemia due to carcinoma. *Br. J. med. J.*, 14–19.

Thiebaud, D., Jaeger, P., Jacquet, A. F. & Burckhardt, P. (1986a). A single-day treatment of tumor-induced hypercalcemia by intravenous amino-hydroxypropylidene bisphosphonate. *J. Bone Miner. Res.*, **6**, 555–562.

Thiebaud, D., Portmann, L., Jaegar, Ph., Jacquet, A. F. & Burckhardt, P. (1986b). Oral versus intravenous AHPrBP (APD) in the treatment of hypercalcemia of malignancy. *Bone*, **7**, 247–253.

van Breukelen, F. J. M., Bijvoet, O. L. M., Frijlink, W. B., Sleeboom, H. P., Mulder, H. & Van Oosterom, A. T. (1982). Efficacy of amino-hydroxypropylidene bisphosphonate in hypercalcemia: Observations on regulation of serum calcium. *Calcif. Tiss. Int.*, **34**, 321–327.

Verenr, J. V., Engel, F. L. & McPherson, H. T. (1958). Vitamin D intoxication: report of two cases treated with cortisone. *Ann. Intern. Med.*, **48**, 765–766.

Warrell, R. P., Bockman, R. S., Coonley, C. J., Isaacs, M. & Staszewski, H. (1984). Gallium nitrate inhibits calcium resorption from bone and is effective treatment for cancer-related hypercalcemia. *J. clin. Invest.*, **73**, 1487–1490.

Warrell, R. P., Coonley, C. J., Straus, D. J. & Young, C. W. (1983). Treatment of patients with advanced malignant lymphoma using gallium nitrate administered as a seven day continuous infusion. *Cancer*, **51**, 1982–1987.

Warrell, R. P., Israel, R., Frisone, M., Snyder, T., Gayner, J. J. & Bockman, R. S. (1988). Gallium nitrate for acute treatment of cancer-related hypercalcemia. *Ann. intern. Med.*, **108**, 669–674.

Warrell, R. P., Murphy, W. K., Schulman, P. J. & O'Dwyer, P. J. (1990). Gallium nitrate for treatment of cancer-related hypercalcemia: a randomized double-blind comparison to etidronate. *J. clin. Oncol.*, **9**, 65–69.

Warwick, O. H., Yendt, E. R. & Olin, J. S. (1961). The clinical features of hypercalcemia associated with malignant disease. *Can. med. Ass. J.*, **23**, 719–723.

Watson, L., Moxham, J. & Fraser, P. (1980). Hydrocortisone suppression test and discriminant analysis in differential diagnosis of hypercalcaemia. *Lancet*, **i**, 1320–1325.

Weidmann, P., Massry, S. G., Coburn, J. W., Maxwell, M. H., Atleson, J. & Kleeman, C. R. (1972). Blood pressure effects of acute hypercalcemia. *Ann. intern. Med.*, **76**, 741–745.

Wisneski, L. A., Croom, W. P., Silva, O. L. & Becker, K. L. (1978). Salmon calcitonin in hypercalcemia. *Clin. Pharmac. Ther.*, **24**, 219–222.

Witte, R. S., Koeller, J., Davis, T. E., Benson, A. B., Durie, B. G., Lipton, A., Stock, J. L., Citrin, D. L. & Jacobs, T. P. (1987). Clodronate: A randomized study in the treatment of cancer-related hypercalcemia. *Arch. Int. Med.*, **147**, 937–939.

Wynick, D., Ratcliffe, W. A., Heath, D. A., Ball, S., Barnard, M. & Bloom, S. R. (1990). Treatment of a malignant pancreatic endocrine tumour secreting parathyroid hormone-related protein. *Br. med. J.*, **300**, 1314–1315.

Yates, A. J. P., Jones, T. H., Mundy, K. I., Hague, R. V., Brown, C. B., Guilland-Cumming, D. & Kanis, J. A. (1984). Immobilisation hypercalcaemia in adults and treatment with clodronate. *Br. med. J.*, **289**, 1111–1112.

Yates, A. J. P., Jerums, G. J., Murray, R. M. L. & Martin, T. J. (1987). A comparison of single and multiple intravenous infusions of 3-amino-1-hydroxypropylidene-1, 1-bisphosphonate (APD) in the treatment of hypercalcemia of malignancy. *Aust. N.Z. J. Med.*, **17**, 387–391.

(Received 15 October 1991, accepted 14 February 1992)